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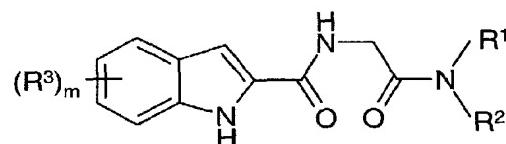
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(54) Title: CHEMICAL COMPOUNDS



(1)

(57) Abstract: Heterocyclic amides of formula (1) (A chemical formula should be inserted here - please see paper copy enclosed herewith) (1) wherein: R¹ is independently selected from, for example, C₁₋₆alkyl, C₅₋₇cycloalkyl, C₅₋₇cycloalkylC₁₋₃alkyl, C₁₋₆alkoxy, C₅₋₇cycloalkoxy, C₅₋₇cycloalkylC₁₋₃alkoxy, heterocyclyl, heterocyclylC₁₋₃alkyl, heterocyclolxy or heterocyclylC₁₋₃alkoxy; R² is phenyl or heteroaryl; R³ is independently selected from hydrogen, halo, nitro, cyano, hydroxy, carboxy, carbamoyl, C₁₋₄alkyl, C₂₋₄alkenyl, C₂₋₄alkynyl, C₁₋₄alkoxy, C₁₋₄alkanoyl, fluoromethyl, difluoromethyl, trifluoromethyl and trifluoromethoxy; or a pharmaceutically acceptable salt or pro-drug thereof; possess glycogen phosphorylase inhibitory activity and accordingly have value in the treatment of disease states associated with increased glycogen phosphorylase activity. Processes for the manufacture of said heterocyclic amide derivatives and pharmaceutical compositions containing them are described.

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CHEMICAL COMPOUNDS

The present invention relates to heterocyclic amide derivatives, pharmaceutically acceptable salts and *in vivo* hydrolysable esters thereof. These heterocyclic amide possess 5 glycogen phosphorylase inhibitory activity and accordingly have value in the treatment of disease states associated with increased glycogen phosphorylase activity and thus are potentially useful in methods of treatment of a warm-blooded animal such as man. The invention also relates to processes for the manufacture of said heterocyclic amide derivatives, to pharmaceutical compositions containing them and to their use in the manufacture of 10 medicaments to inhibit glycogen phosphorylase activity in a warm-blooded animal such as man.

The liver is the major organ regulating glycaemia in the post-absorptive state. Additionally, although having a smaller role in the contribution to post-prandial blood glucose levels, the response of the liver to exogenous sources of plasma glucose is key to an ability to 15 maintain euglycaemia. An increased hepatic glucose output (HGO) is considered to play an important role in maintaining the elevated fasting plasma glucose (FPG) levels seen in type 2 diabetics; particularly those with a FPG >140mg/dl (7.8mM). (Weyer et al, (1999), J Clin Invest 104: 787-794; Clore & Blackgard (1994), Diabetes 43: 256-262; De Fronzo, R. A., et al, (1992) Diabetes Care 15; 318 - 355; Reaven, G.M. (1995) Diabetologia 38; 3-13).

20 Since current oral, anti-diabetic therapies fail to bring FPG levels to within the normal, non-diabetic range and since raised FPG (and glycHbA1c) levels are risk factors for both macro- (Charles, M.A. et al (1996) Lancet 348, 1657-1658; Coutinho, M. et al (1999) Diabetes Care 22; 233-240; Shaw, J.E. et al (2000) Diabetes Care 23, 34-39) and micro-vascular disease (DCCT Research Group (1993) New. Eng. J. Med. 329; 977-986); the 25 reduction and normalisation of elevated FPG levels remains a treatment goal in type 2 DM.

It has been estimated that, after an overnight fast, 74% of HGO was derived from glycogenolysis with the remainder derived from gluconeogenic precursors (Hellerstein et al (1997) Am J Physiol, 272: E163). Glycogen phosphorylase is a key enzyme in the generation by glycogenolysis of glucose-1-phosphate, and hence glucose in liver and also in other tissues 30 such as muscle and neuronal tissue.

Liver glycogen phosphorylase a activity is elevated in diabetic animal models including the db/db mouse and the fa/fa rat (Aiston S et al (2000). Diabetologia 43, 589-597).

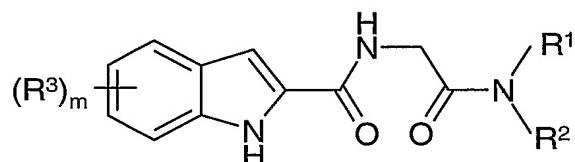
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Inhibition of hepatic glycogen phosphorylase with chloroindole inhibitors (CP91149 and CP320626) has been shown to reduce both glucagon stimulated glycogenolysis and glucose output in hepatocytes (Hoover et al (1998) J Med Chem 41, 2934-8; Martin et al (1998) PNAS 95, 1776-81). Additionally, plasma glucose concentration is reduced, in a dose related manner, db/db and ob/ob mice following treatment with these compounds.

Studies in conscious dogs with glucagon challenge in the absence and presence of another glycogen phosphorylase inhibitor, Bay K 3401, also show the potential utility of such agents where there is elevated circulating levels of glucagon, as in both Type 1 and Type 2 diabetes. In the presence of Bay R 3401, hepatic glucose output and arterial plasma glucose following a glucagon challenge were reduced significantly (Shiota et al, (1997), Am J Physiol, 273: E868).

The heterocyclic amides of the present invention possess glycogen phosphorylase inhibitory activity and accordingly are expected to be of use in the treatment of type 2 diabetes, insulin resistance, syndrome X, hyperinsulinaemia, hyperglucagonaemia, cardiac ischaemia and obesity, particularly type 2 diabetes.

According to one aspect of the present invention there is provided a compound of formula (1):



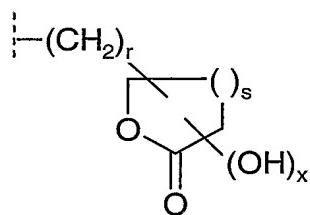
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(1)

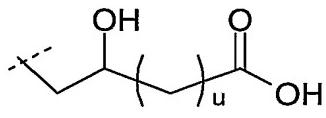
wherein:

R¹ is independently selected from C₁₋₆alkyl, C₅₋₇cycloalkyl, C₅₋₇cycloalkylC₁₋₃alkyl, C₁₋₆alkoxy, C₅₋₇cycloalkoxy, C₅₋₇cycloalkylC₁₋₃alkoxy, heterocyclyl, heterocyclylC₁₋₃alkyl, heterocycloloxy or heterocyclylC₁₋₃alkoxy (wherein each of these groups is substituted on 25 carbon by 1, 2 or 3 hydroxy groups, provided that there is no more than one hydroxy group on the same carbon atom and a ring carbon atom adjacent to a ring heteroatom is not substituted by a hydroxy group) and groups of the formula A or A':

-3-



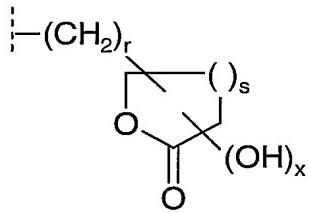
(A)



(A')

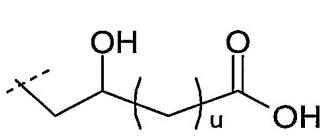
wherein x is 0 or 1, r is 0, 1, 2 or 3, s is 1 or 2 and u is 1 or 2; provided that in (A) the hydroxy group is not a substituent on the ring carbon adjacent to the ring oxygen;

- 5 R^2 is phenyl or heteroaryl (each of which is optionally substituted by 1 or 2 substituents independently selected from halo, cyano, trifluoromethyl, difluoromethyl, fluoromethyl, C_{1-3} alkoxy, C_{1-3} alkanoyl, carbamoyl, N - C_{1-3} alkylcarbamoyl, N,N -di- C_{1-3} alkylcarbamoyl, sulfamoyl, N - C_{1-3} alkylsulfamoyl, N,N -di- C_{1-3} alkylsulfamoyl and groups of the formulae B and B':



10

(B)



(B')

wherein x is 0 or 1, r is 0, 1, 2 or 3, s is 1 or 2 and u is 1 or 2; provided that the hydroxy group is not a substituent on the ring carbon adjacent to the ring oxygen);

m is 0, 1 or 2;

- 15 R^3 is independently selected from hydrogen, halo, nitro, cyano, hydroxy, carboxy, carbamoyl, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} alkoxy, C_{1-4} alkanoyl, fluoromethyl, difluoromethyl, trifluoromethyl and trifluoromethoxy;

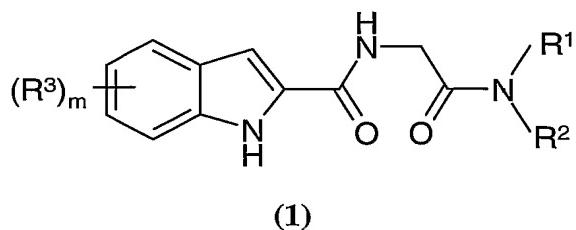
provided that when R^1 is of the formula A or A' then R^2 does not contain a group of the formula B or B' and when R^2 is of the formula B or B' then R^1 does not contain a group of the

- 20 formula A or A';

or a pharmaceutically acceptable salt or prodrug thereof.

According to another aspect of the present invention there is provided a compound of formula (1):

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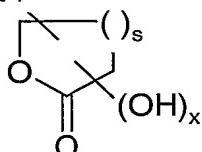


wherein:

R¹ is C₁₋₆alkyl, C₅₋₇cycloalkyl, C₅₋₇cycloalkylC₁₋₃alkyl, C₁₋₆alkoxy, C₅₋₇cycloalkoxy,

- 5 C₅₋₇cycloalkylC₁₋₃alkoxy, heterocyclyl, heterocyclylC₁₋₃alkyl, heterocyclyloxy or heterocyclylC₁₋₃alkoxy (wherein each of these groups is substituted on carbon by 1, 2 or 3 hydroxy groups, provided that there is no more than one hydroxy group on the same carbon atom and a ring carbon atom adjacent to a ring heteroatom is not substituted by a hydroxy group) or R¹ is of the formula A or A':

$$-(\text{CH}_2)_n-$$



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(A)

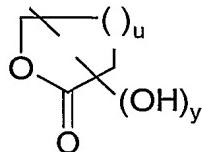
$$-\text{CH}_2\text{CH}(\text{OH})(\text{CH}_2)_u\text{CO}_2\text{H} \quad (\text{A}')$$

wherein **x** is 0 or 1, **r** is 0, 1, 2 or 3 and **s** is 1 or 2; provided that the hydroxy group is not a substituent on the ring carbon adjacent to the ring oxygen;

\mathbf{R}^2 is phenyl or heteroaryl (each of which is optionally substituted by 1 or 2 substituents)

independently selected from halo, cyano, trifluoromethyl, difluoromethyl, fluoromethyl, C₁₋₃alkoxy, C₁₋₃alkanoyl, carbamoyl, N-C₁₋₃alkylcarbamoyl, N,N-di-C₁₋₃alkylcarbamoyl, sulfamoyl, N-C₁₋₃alkylsulfamoyl, N,N-di-C₁₋₃alkylsulfamoyl and groups of the formulae B and B':

$$-(\text{CH}_2)_t-$$



(B)

$$-\text{CH}_2\text{CH(OH)(CH}_2\text{)}_u\text{CO}_2\text{H (B')}$$

wherein **y** is 0 or 1, **t** is 0, 1, 2 or 3 and **u** is 1 or 2; provided that the hydroxy group is not a substituent on the ring carbon adjacent to the ring oxygen);

m is 0, 1 or 2;

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C_{1-4} alkylsulphamoyl, N,N -di(C_{1-4} alkyl)sulphamoyl, sulfino, sulfo, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} alkoxy, C_{1-4} alkanoyl, C_{1-4} alkanoyloxy, N -(C_{1-4} alkyl)amino, N,N -di-(C_{1-4} alkyl)amino, hydroxy C_{1-4} alkyl, fluoromethyl, difluoromethyl, trifluoromethyl and trifluoromethoxy ;

- 5 provided that when R^1 is of the formula A or A' then R^2 does not contain a group of the formula B or B' and when R^2 is of the formula B or B' then R^1 does not contain a group of the formula A or A';
or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof.

10 In another aspect, the invention relates to compounds of formula (1) as hereinabove defined or to a pharmaceutically acceptable salt.

In another aspect, the invention relates to compounds of formula (1) as hereinabove defined or to a pro-drug thereof. Suitable examples of pro-drugs of compounds of formula (1) are *in-vivo* hydrolysable esters of compounds of formula (1). Therefore in another aspect, the
15 invention relates to compounds of formula (1) as hereinabove defined or to an *in-vivo* hydrolysable ester thereof.

It is to be understood that, insofar as certain of the compounds of formula (1) defined above may exist in optically active or racemic forms by virtue of one or more asymmetric carbon atoms, the invention includes in its definition any such optically active or racemic
20 form which possesses glycogen phosphorylase inhibition activity. The synthesis of optically active forms may be carried out by standard techniques of organic chemistry well known in the art, for example by synthesis from optically active starting materials or by resolution of a racemic form. Similarly, the above-mentioned activity may be evaluated using the standard laboratory techniques referred to hereinafter.

25 Within the present invention it is to be understood that a compound of the formula (1) or a salt thereof may exhibit the phenomenon of tautomerism and that the formulae drawings within this specification can represent only one of the possible tautomeric forms. It is to be understood that the invention encompasses any tautomeric form, which has glycogen phosphorylase inhibition activity and is not to be limited merely to any one tautomeric form
30 utilised within the formulae drawings. The formulae drawings within this specification can represent only one of the possible tautomeric forms and it is to be understood that the specification encompasses all possible tautomeric forms of the compounds drawn not just

those forms which it has been possible to show graphically herein.

It is also to be understood that certain compounds of the formula (1) and salts thereof can exist in solvated as well as unsolvated forms such as, for example, hydrated forms. It is to be understood that the invention encompasses all such solvated forms which have glycogen phosphorylase inhibition activity.

It is also to be understood that certain compounds of the formula (1) may exhibit polymorphism, and that the invention encompasses all such forms which possess glycogen phosphorylase inhibition activity.

The present invention relates to the compounds of formula (1) as hereinbefore defined as well as to the salts thereof. Salts for use in pharmaceutical compositions will be pharmaceutically acceptable salts, but other salts may be useful in the production of the compounds of formula (1) and their pharmaceutically acceptable salts. Pharmaceutically acceptable salts of the invention may, for example, include acid addition salts of the compounds of formula (1) as hereinbefore defined which are sufficiently basic to form such salts. Such acid addition salts include for example salts with inorganic or organic acids affording pharmaceutically acceptable anions such as with hydrogen halides (especially hydrochloric or hydrobromic acid of which hydrochloric acid is particularly preferred) or with sulphuric or phosphoric acid, or with trifluoroacetic, citric or maleic acid. Suitable salts include hydrochlorides, hydrobromides, phosphates, sulphates, hydrogen sulphates, alkylsulphonates, arylsulphonates, acetates, benzoates, citrates, maleates, fumarates, succinates, lactates and tartrates. In addition where the compounds of formula (1) are sufficiently acidic, pharmaceutically acceptable salts may be formed with an inorganic or organic base which affords a pharmaceutically acceptable cation. Such salts with inorganic or organic bases include for example an alkali metal salt, such as a sodium or potassium salt, an alkaline earth metal salt such as a calcium or magnesium salt, an ammonium salt or for example a salt with methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine.

The compounds of the invention may be administered in the form of a pro-drug which is broken down in the human or animal body to give a compound of the invention. A prodrug may be used to alter or improve the physical and/or pharmacokinetic profile of the parent compound and can be formed when the parent compound contains a suitable group or substituent which can be derivatised to form a prodrug. Examples of pro-drugs include in-

vivo hydrolysable esters of a compound of the invention or a pharmaceutically-acceptable salt thereof.

Various forms of prodrugs are known in the art, for examples see:

- a) Design of Prodrugs, edited by H. Bundgaard, (Elsevier, 1985) and Methods in Enzymology, Vol. 42, p. 309-396, edited by K. Widder, *et al.* (Academic Press, 1985);
- 5 b) A Textbook of Drug Design and Development, edited by Krosgaard-Larsen and H. Bundgaard, Chapter 5 "Design and Application of Prodrugs", by H. Bundgaard p. 113-191 (1991);
- c) H. Bundgaard, Advanced Drug Delivery Reviews, 8, 1-38 (1992);
- 10 d) H. Bundgaard, *et al.*, Journal of Pharmaceutical Sciences, 77, 285 (1988); and
- e) N. Kakeya, *et al.*, Chem Pharm Bull, 32, 692 (1984).

An *in vivo* hydrolysable ester of a compound of formula (1) containing carboxy or hydroxy group is, for example. A pharmaceutically acceptable ester which is cleaved in the 15 human or animal body to produce the parent acid or alcohol.

Suitable pharmaceutically acceptable esters for carboxy include C₁₋₆alkoxymethyl esters for example methoxymethyl, C₁₋₆alkanoyloxymethyl esters for example pivaloyloxymethyl, phthalidyl esters, C₃₋₈cycloalkoxycarbonyloxyC₁₋₆alkyl esters for example 1-cyclohexylcarbonyloxyethyl; 1,3-dioxolen-2-onylmethyl esters for example 20 5-methyl-1,3-dioxolen-2-onylmethyl; and C₁₋₆alkoxycarbonyloxyethyl esters for example 1-methoxycarbonyloxyethyl and may be formed at any carboxy group in the compounds of this invention.

Suitable pharmaceutically-acceptable esters for hydroxy include inorganic esters such as phosphate esters (including phosphoramidic cyclic esters) and α -acyloxyalkyl ethers and 25 related compounds which as a result of the *in-vivo* hydrolysis of the ester breakdown to give the parent hydroxy group/s. Examples of α -acyloxyalkyl ethers include acetoxymethoxy and 2,2-dimethylpropionyloxymethoxy. A selection of *in-vivo* hydrolysable ester forming groups for hydroxy include C₁₋₁₀alkanoyl, for example acetyl; benzoyl; phenylacetyl; substituted benzoyl and phenylacetyl, C₁₋₁₀alkoxycarbonyl (to give alkyl carbonate esters), for example 30 ethoxycarbonyl; di-(C₁₋₄)alkylcarbamoyl and *N*-(di-(C₁₋₄)alkylaminoethyl)-*N*-(C₁₋₄)alkylcarbamoyl (to give carbamates); di-(C₁₋₄)alkylaminoacetyl and carboxyacetyl. Examples of ring substituents on phenylacetyl and benzoyl include aminomethyl, (C₁₋

4) alkylaminomethyl and di-((C₁₋₄)alkyl)aminomethyl, and morpholino or piperazino linked from a ring nitrogen atom via a methylene linking group to the 3- or 4- position of the benzoyl ring. Other interesting in-vivo hydrolysable esters include, for example, R^AC(O)O(C₁₋₆)alkyl-CO-, wherein R^A is for example, benzyloxy-(C₁₋₄)alkyl, or phenyl). Suitable substituents on a 5 phenyl group in such esters include, for example, 4-(C₁₋₄)piperazino-(C₁₋₄)alkyl, piperazino-(C₁₋₄)alkyl and morpholino-(C_{1-C4})alkyl.

In this specification the generic term “alkyl” includes both straight-chain and branched-chain alkyl groups. However references to individual alkyl groups such as “propyl” are specific for the straight chain version only and references to individual branched-chain 10 alkyl groups. For example, “C₁₋₆alkyl” and “C₁₋₄alkyl” include propyl, isopropyl and t-butyl. An analogous convention applies to other generic terms, for example “hydroxyC₁₋₄alkyl” includes 2-hydroxyethyl, 1-hydroxyethyl and hydroxymethyl. The term “halo” refers to fluoro, chloro, bromo and iodo.

A “heterocyclic group” is an optionally substituted saturated, monocyclic ring 15 containing 5-7 ring atoms of which at least 1, 2 or 3 ring atoms are chosen from nitrogen, sulphur or oxygen, and which may, unless otherwise specified, be carbon or nitrogen linked, wherein a -CH₂- group can optionally be replaced by a -C(O)- and a ring sulphur atom may be optionally oxidised to form the S-oxide(s). Examples and suitable values of the term “heterocyclic group” are morpholino, 1,3-dioxolanyl, morpholinyl, piperidino and piperidyl. 20 A particular example of a “heterocyclic group” is morpholinyl.

Suitable optional substituents for “heterocyclyl” as a saturated or partially saturated ring are 1, 2 or 3 substituents independently selected from halo, cyano, hydroxy, C₁₋₄alkyl, C₁₋₄alkoxy and C₁₋₄alkylS(O)_b (wherein b is 0, 1 or 2). Further suitable substituents for 25 “heterocyclyl” as a saturated or partially saturated ring are 1, 2 or 3 substituents independently selected from fluoro, chloro, cyano, hydroxy, methyl, ethyl, methoxy, methylthio, methylsulfinyl and methylsulfonyl.

Suitable optional substituents for “heterocyclyl” as an unsaturated ring are 1, 2 or 3 substituents independently selected from halo, cyano, nitro, amino, hydroxy, C₁₋₄alkyl, C₁₋₄alkoxy, C₁₋₄alkylS(O)_b (wherein b is 0, 1 or 2), N-(C₁₋₄alkyl)amino and 30 N,N-(C₁₋₄alkyl)₂amino. Further suitable optional substituents for “heterocyclyl” as an unsaturated ring are 1, 2 or 3 substituents independently selected from fluoro, chloro, cyano,

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nitro, amino, methylamino, dimethylamino, hydroxy, methyl, ethyl, methoxy, methylthio, methylsulfinyl and methylsulfonyl.

A heteroaryl group is an aryl monocyclic ring system containing 5 to 7 ring atoms of which 1, 2, 3 or 4 (in particular 1, 2 or 3) ring atoms are chosen from nitrogen, sulphur or 5 oxygen, and which may, unless otherwise specified, be carbon or nitrogen linked. Particular heteroaryl rings are pyridyl, oxadiazolyl, oxazolyl, thiazolyl, thieryl, pyrimidyl, thiadiazolyl, isothiadiazolyl and isoxazolyl.

Suitable optional substituents for “heteroaryl” are, unless otherwise stated, 1, 2 or 3 substituents independently selected from halo, cyano, nitro, amino, hydroxy, C₁₋₄alkyl, C₁₋₁₀alkoxy, C₁₋₄alkylS(O)_b (wherein b is 0, 1 or 2), N-(C₁₋₄alkyl)amino and N,N-(C₁₋₄alkyl)₂amino. Further suitable optional substituents for “heterocycl” as an unsaturated ring are 1, 2 or 3 substituents independently selected from fluoro, chloro, cyano, nitro, amino, methylamino, dimethylamino, hydroxy, methyl, ethyl, methoxy, methylthio, methylsulfinyl and methylsulfonyl.

15 Examples of “(heterocycl)C₁₋₄alkyl” are morpholinomethyl, morpholinethyl, morpholinylmethyl, morpholinylethyl, piperidinomethyl, piperidinoethyl, piperidylmethyl, piperidylethyl, imidazolylmethyl, imidazolylethyl, oxazolylmethyl, oxazolylethyl, 1,3,4-oxadiazolylmethyl, 1,2,4-oxadiazolylmethyl, 1,2,4-oxadiazolylethyl, pyridylmethyl, pyridylethyl, furylmethyl, furylethyl, (thienyl)methyl, (thienyl)ethyl, pyrazinylmethyl, 20 pyrazinylethyl, piperazinylmethyl and piperazinylethyl.

Examples of “aryl” are optionally substituted phenyl and naphthyl.

Examples of “aryl(C₁₋₄)alkyl” are benzyl, phenethyl, naphthylmethyl and naphthylethyl.

Suitable optional substituents for “aryl” groups are, unless otherwise stated, 1, 2 or 3 substituents independently selected from halo, cyano, nitro, amino, hydroxy, C₁₋₄alkyl, C₁₋₄alkoxy, C₁₋₄alkylS(O)_b (wherein b is 0, 1 or 2), N-(C₁₋₄alkyl)amino and N,N-(C₁₋₄alkyl)₂amino. Further suitable optional substituents for “aryl” groups are 1, 2 or 3 substituents independently selected from fluoro, chloro, cyano, nitro, amino, methylamino, dimethylamino, hydroxy, methyl, ethyl, methoxy, methylthio, methylsulfinyl and 30 methylsulfonyl.

Where optional substituents are chosen from “0, 1, 2 or 3” groups it is to be understood that this definition includes all substituents being chosen from one of the specified

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groups or the substituents being chosen from two or more of the specified groups. An analogous convention applies to substituents chose from “0, 1 or 2” groups and “1 or 2” groups.

- There following are particular and suitable values for certain substituents and groups referred to in this specification. These values may be used where appropriate with any of the definitions and embodiments disclosed hereinbefore, or hereinafter. For the avoidance of doubt each stated species represents a particular and independent aspect of this invention.
- Examples of “C₁₋₆alkyl” and “C₁₋₄alkyl” include methyl, ethyl and propyl.
- Examples of “hydroxyC₁₋₄alkyl” include hydroxymethyl, 2-hydroxyethyl and 2-hydroxypropyl.
- Examples of “C₁₋₆alkoxy” and “C₁₋₄alkoxy” include methoxy, ethoxy and propoxy.
- Examples of “C₁₋₃alkanoyl” and “C₁₋₄alkanoyl” include acetyl and propionyl.
- Examples of “N-(C₁₋₆alkyl)sulphamoyl” are N-(methyl)sulphamoyl and N-(ethyl)sulphamoyl.
- Examples of “N, N-di-(C₁₋₆alkyl)sulphamoyl” are N,N-(dimethyl)sulphamoyl and N-(methyl)-N-(ethyl)sulphamoyl.
- Examples of “N-(C₁₋₆alkyl)carbamoyl” are N-(C₁₋₄alkyl)carbamoyl, methylaminocarbonyl and ethylaminocarbonyl.
- Examples of “N,N-di-(C₁₋₆alkyl)carbamoyl” are N,N-(C₁₋₄alkyl)carbamoyl, dimethylaminocarbonyl and methylethylaminocarbonyl.
- Examples of “C₁₋₄alkanoyloxy” include acetyloxy and propionyloxy.
- Examples of “C₂₋₄alkenyl” include vinyl, allyl and 1-propenyl.
- Examples of “C₂₋₄alkynyl” include ethynyl and 1-propynyl.
- Examples of “N-(C₁₋₄alkyl)amino” are methylamino and ethylamino.
- Examples of “N,N-di-(C₁₋₄alkyl)amino” are dimethylamino and methylethylamino.
- Examples of “C₅₋₇cycloalkyl ring” are cyclopentyl and cyclohexyl.
- Examples of “dihaloC₁₋₄alkyl” are difluoromethyl and dichloromethyl.
- Example of “trihaloC₁₋₄alkyl” is trifluoromethyl.
- The term “sulfo” means HOSO₂⁻. The term “sulfino” means HO₂S⁻.
- Particular values of R¹, R², R³ and m are as follows. Such values may be used where appropriate with any of the definitions, claims or embodiments defined hereinbefore or hereinafter.

In one embodiment of the invention are provided compounds of formula (1), in an

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alternative embodiment are provided pharmaceutically-acceptable salts of compounds of formula (1), in a further alternative embodiment are provided in-vivo hydrolysable esters of compounds of formula (1), and in a further alternative embodiment are provided pharmaceutically-acceptable salts of in-vivo hydrolysable esters of compounds of formula (1).

5 In one aspect R¹ is C₁₋₆alkyl, C₅₋₇cycloalkyl, C₅₋₇cycloalkylmethyl, C₁₋₆alkoxy, C₅₋₇cycloalkoxy, C₅₋₇cycloalkylC₁₋₃methoxy, heterocyclyl, heterocyclylmethyl, heterocyclcloxy or heterocyclylmethoxy (each group is substituted by 1 or 2 hydroxy groups provided that there is no more than one hydroxy group on the same carbon atom) or R¹ is of the formula A or A' as hereinabove defined.

10 In another aspect R¹ is C₁₋₆alkyl, C₅₋₇cycloalkyl, C₅₋₇cycloalkylmethyl, C₁₋₆alkoxy, C₅₋₇cycloalkoxy, C₅₋₇cycloalkylC₁₋₃methoxy, heterocyclyl, heterocyclylmethyl, heterocyclcloxy or heterocyclylmethoxy (each group is substituted by 1 or 2 hydroxy groups provided that there is no more than one hydroxy group on the same carbon atom).

15 In another aspect R¹ is C₁₋₆alkyl, C₅₋₇cycloalkyl, C₅₋₇cycloalkylmethyl, C₁₋₆alkoxy, C₅₋₇cycloalkoxy or C₅₋₇cycloalkylC₁₋₃methoxy, (each group is substituted by 1 or 2 hydroxy groups provided that there is no more than one hydroxy group on the same carbon atom).

In yet another aspect, R¹ is ethyl, propyl, cyclopentyl, cyclohexyl, cyclopentylmethyl or cyclohexylmethyl (wherein each group is substituted by 1 or 2 hydroxy groups provided that there is no more than one hydroxy group on the same carbon atom).

20 In yet another aspect, R¹ is 2-hydroxyethyl, 2,3-dihydroxypropyl, 3,4-dihydroxycyclopentyl or 3,4-dihydroxycyclopentylmethyl.

In one aspect, R² is heteroaryl.

Particular heteroaryl rings are pyridyl, oxadiazolyl, oxazolyl, thiazolyl, thienyl, pyrimidyl, thiadiazolyl, isothiadiazolyl and isoxazolyl.

25 More particular heteroaryl rings are pyridyl, oxadiazolyl, oxazolyl, thiazolyl and thienyl.

In another aspect, R² is phenyl.

In one aspect the phenyl or heteroaryl group in R² is optionally substituted by 1 or 2 substituents independently selected from halo, cyano, trifluoromethyl, carbamoyl, N-C₁₋₃alkylcarbamoyl, N,N-di-C₁₋₃alkylcarbamoyl, sulfamoyl, N-C₁₋₃alkylsulfamoyl, N,N-di-C₁₋₃alkylsulfamoyl, a group of the formula B and a group of the formula B' as hereinabove defined.

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In another aspect the phenyl or heteroaryl group in R² is optionally substituted by 1 or 2 substituents independently selected from halo, cyano, trifluoromethyl, carbamoyl, N-C₁-3alkylcarbamoyl, N,N-di-C₁-3alkylcarbamoyl, sulfamoyl, N-C₁-3alkylsulfamoyl, N,N-di-C₁-3alkylsulfamoyl.

5 In another aspect, the phenyl or heteroaryl group in R² is optionally substituted by 1 or 2 substituents independently selected from halo, cyano, trifluoromethyl, carbamoyl, N-C₁-3alkylcarbamoyl, sulfamoyl and N-C₁-3alkylsulfamoyl.

10 In yet another aspect, the phenyl or heteroaryl group in R² is optionally substituted by 1 or 2 substituents independently selected from fluoro, chloro, cyano, trifluoromethyl, carbamoyl and sulfamoyl.

In yet another aspect, the phenyl or heteroaryl group in R² is unsubstituted or substituted by 1 fluoro substituent.

In yet another aspect, the phenyl or heteroaryl group in R² is unsubstituted.

In one aspect of the present invention m is 1 or 2.

15 In another aspect of the invention m is 1.

In yet another aspect m is 0.

In one aspect of the present invention R³ is selected from hydrogen, halo, cyano, hydroxy, fluoromethyl, difluoromethyl and trifluoromethyl.

In another aspect of the invention R³ is hydrogen or halo.

20 Preferably R³ is selected from hydrogen, chloro or bromo.

More preferably R³ is chloro.

In another aspect, the invention relates to a class of compounds of the formula (1) wherein:

R¹ is selected from C₁-6alkyl, C₅-7cycloalkyl, C₅-7cycloalkylmethyl, C₁-6alkoxy,

25 C₅-7cycloalkoxy, C₅-7cycloalkylC₁-3methoxy, heterocyclyl, heterocyclylmethyl, heterocycloloxy and heterocyclylmethoxy (wherein each of these groups is substituted by 1 or 2 hydroxy groups provided that there is no more than one hydroxy group on the same carbon atom) or R¹ is of the formula A or A' as hereinabove defined;

R² is a phenyl or heteroaryl group (each of which is optionally substituted by 1 or 2

30 substituents independently selected from halo, cyano, trifluoromethyl, carbamoyl, N-C₁-3alkylcarbamoyl, N,N-di-C₁-3alkylcarbamoyl, sulfamoyl, N-C₁-3alkylsulfamoyl,

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N,N-di-C₁₋₃alkylsulfamoyl, a group of the formula B and a group of the formula B' as hereinabove defined);

and m and R³ are as hereinabove defined;

provided that when R¹ is of the formula A or A' then R² does not contain a group of the

5 formula B or B' and when R² is of the formula B or B' then R¹ does not contain a group of the formula A or A';

or a pharmaceutically-acceptable salt or in-vivo hydrolysable ester thereof.

In yet another aspect, the invention relates to a class of compounds of the formula (1) wherein:

10 R¹ is selected from C₁₋₆alkyl, C₅₋₇cycloalkyl, C₅₋₇cycloalkylmethyl, C₁₋₆alkoxy, C₅₋₇cycloalkoxy and C₅₋₇cycloalkylC₁₋₃methoxy, (each group is substituted by 1 or 2 hydroxy groups provided that there is no more than one hydroxy group on the same carbon atom); R² is a phenyl or heteroaryl group (each of which is optionally substituted by 1 or 2 substituents independently selected from halo, cyano, trifluoromethyl, carbamoyl,

15 N-C₁₋₃alkylcarbamoyl, N,N-di-C₁₋₃alkylcarbamoyl, sulfamoyl, N-C₁₋₃alkylsulfamoyl and N,N-di-C₁₋₃alkylsulfamoyl);

and m and R³ are as hereinabove defined;

or a pharmaceutically-acceptable salt or in-vivo hydrolysable ester thereof.

In yet another aspect, the invention relates to a class of compounds of the formula (1)

20 wherein:

R¹ is selected from C₁₋₆alkyl, C₅₋₇cycloalkyl, C₅₋₇cycloalkylmethyl, C₁₋₆alkoxy, C₅₋₇cycloalkoxy and C₅₋₇cycloalkylC₁₋₃methoxy, (each group is substituted by 1 or 2 hydroxy groups provided that there is no more than one hydroxy group on the same carbon atom);

R² is a phenyl or heteroaryl group (each of which is optionally substituted by 1 or 2

25 substituents independently selected from halo, cyano, trifluoromethyl, carbamoyl, N-C₁₋₃alkylcarbamoyl, N,N-di-C₁₋₃alkylcarbamoyl, sulfamoyl, N-C₁₋₃alkylsulfamoyl and N,N-di-C₁₋₃alkylsulfamoyl);

m is as hereinabove defined; and

R³ is selected from hydrogen, halo, cyano, hydroxy, fluoromethyl, difluoromethyl and

30 trifluoromethyl;

or a pharmaceutically-acceptable salt or in-vivo hydrolysable ester thereof.

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In yet another aspect, the invention relates to a class of compounds of the formula (1) wherein:

R¹ is selected from C₁₋₆alkyl, C₅₋₇cycloalkyl, C₅₋₇cycloalkylmethyl, C₁₋₆alkoxy,

C₅₋₇cycloalkoxy and C₅₋₇cycloalkylC₁₋₃methoxy, (each group is substituted by 1 or 2 hydroxy

5 groups provided that there is no more than one hydroxy group on the same carbon atom);

R² is selected from phenyl, pyridyl, oxadiazolyl, oxazolyl, thiazolyl and thieryl (each of which is optionally substituted by 1 or 2 substituents independently selected from halo, cyano, trifluoromethyl, carbamoyl, N-C₁₋₃alkylcarbamoyl, sulfamoyl, N-C₁₋₃alkylsulfamoyl and N,N-di-C₁₋₃alkylsulfamoyl);

10 m is 1 or 2; and

R³ is selected from hydrogen, halo, cyano, hydroxy, fluoromethyl, difluoromethyl and trifluoromethyl;

or a pharmaceutically-acceptable salt or in-vivo hydrolysable ester thereof.

In yet another aspect, the invention relates to a class of compounds of the formula (1)

15 wherein:

R¹ is selected from ethyl, propyl, cyclopentyl, cyclohexyl, cyclopentylmethyl and cyclohexylmethyl (wherein each group is substituted by 1 or 2 hydroxy groups provided that there is no more than one hydroxy group on the same carbon atom);

R² is selected from phenyl, pyridyl, oxadiazolyl, oxazolyl, thiazolyl and thieryl (each of which 20 group is optionally substituted by 1 or 2 substituents independently selected from halo, cyano, trifluoromethyl, carbamoyl, N-C₁₋₃alkylcarbamoyl, sulfamoyl and N-C₁₋₃alkylsulfamoyl);

m is 1; and

R³ is chloro;

or a pharmaceutically-acceptable salt or in-vivo hydrolysable ester thereof.

25 In yet another aspect, the invention relates to a class of compounds of the formula (1) wherein:

R¹ is selected from 2-hydroxyethyl, 2,3-dihydroxypropyl, 3,4-dihydroxycyclopentyl and 3,4-dihydroxycyclopentylmethyl;

R² is phenyl optionally substituted by 1 or 2 substituents independently selected from halo,

30 cyano, trifluoromethyl, carbamoyl, N-C₁₋₃alkylcarbamoyl, sulfamoyl and

N-C₁₋₃alkylsulfamoyl;

m is 1 or 2; and

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R^3 is hydrogen or halo;

or a pharmaceutically-acceptable salt or *in-vivo* hydrolysable ester thereof.

A particular compound of the present invention is:

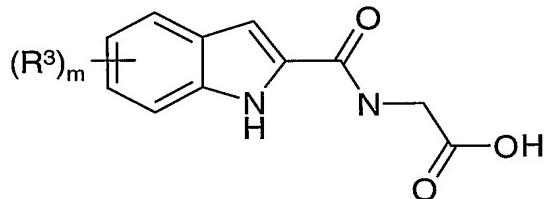
5-chloro-N-{2-[(2-hydroxyethyl)phenylamino]-2-oxoethyl}-1*H*-indole-2-carboxamide;

5 and pharmaceutically-acceptable salts thereof.

Process for Preparing a Compound of Formula (1)

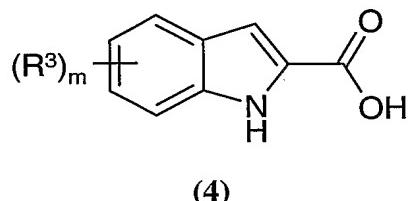
Another aspect of the present invention provides a process for preparing a compound of formula (1) or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof
10 which process comprises:

a) reacting an acid of the formula (2):



or an activated derivative thereof; with an amine of formula (3): HNR^1R^2 or

15 b) reacting an acid of the formula (4):



or an activated derivative thereof; with an amine of formula (5): $H_2NCH_2CONR^1R^2$:

wherein R^1 , R^2 , R^3 and m are, unless otherwise specified, as defined in formula (1);

20 wherein any functional groups are optionally protected;

and thereafter if necessary:

i) converting a compound of the formula (1) into another compound of the formula (1);

ii) removing any protecting groups;

iii) forming a pharmaceutically acceptable salt or *in vivo* hydrolysable ester.

25 Specific reaction conditions for the above reaction are as follows.

Processes a) and b) Acids of formula (2) and amines of formula (3) and acids of

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formula (4) and amines of formula (5) may be coupled together in the presence of a suitable coupling reagent. Standard peptide coupling reagents known in the art can be employed as suitable coupling reagents, or for example 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride, carbonyldiimidazole, 1-ethyl-3-(3-
5 dimethylaminopropyl)carbodi-imide hydrochloride and dicyclohexyl-carbodiimide, optionally in the presence of a catalyst such as 1-hydroxybenzotriazole, dimethylaminopyridine or 4-pyrrolidinopyridine, optionally in the presence of a base for example triethylamine, di-isopropylethylamine, pyridine, or 2,6-di-*alkyl*-pyridines such as 2,6-lutidine or 2,6-di-*tert*-butylpyridine. Suitable solvents include dimethylacetamide, dichloromethane,
10 benzene, tetrahydrofuran and dimethylformamide. The coupling reaction may conveniently be performed at a temperature in the range of -40 to 40°C.

Suitable activated acid derivatives include acid chlorides, for example acid chlorides, and active esters, for example pentafluorophenyl esters. The reaction of these types of compounds with amines is well known in the art, for example they may be reacted in the
15 presence of a base, such as those described above, and in a suitable solvent, such as those described above. The reaction may conveniently be performed at a temperature in the range of -40 to 40°C.

The acids of formula (2) are commercially available or they are known compounds or they are prepared by processes known in the art. For example, an acid of the formula (2) can
20 be formed by reacting together a compound of the formula (4) and a compound of the formula $\text{PO}_2\text{CCH}_2\text{NH}_2$ wherein P is a carboxy-protecting group under conditions described above for amide formation and subsequently removing the protecting group. The acids of formula (2) are commercially available or they are known compounds or they are prepared by processes known in the art.

25 Compounds of formulae (3) and (5) may be prepared by reacting an amine of formula $\text{P}'\text{HNR}^1$, $\text{P}'\text{HNR}^2$, $\text{P}'\text{P}''\text{NCH}_2\text{CONHR}^1$ or $\text{P}'\text{P}''\text{NCH}_2\text{CONHR}^2$ as appropriate with $\text{R}^1\text{-L}$ or $\text{R}^2\text{-L}$, as appropriate, wherein P' and P'' are amino protecting groups and L is a suitable leaving group (for example chloro, bromo or iodo) in the presence of a base such as sodium hydride in a suitable solvent.

30 It will be appreciated that certain of the various ring substituents in the compounds of the present invention may be introduced by standard aromatic substitution reactions or generated by conventional functional group modifications either prior to or immediately

following the processes mentioned above, and as such are included in the process aspect of the invention. Such reactions and modifications include, for example, introduction of a substituent by means of an aromatic substitution reaction, reduction of substituents, alkylation of substituents and oxidation of substituents. The reagents and reaction conditions for such 5 procedures are well known in the chemical art. Particular examples of aromatic substitution reactions include the introduction of a nitro group using concentrated nitric acid, the introduction of an acyl group using, for example, an acyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions; the introduction of an alkyl group using an alkyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts 10 conditions; and the introduction of a halogen group. Particular examples of modifications include the reduction of a nitro group to an amino group by for example, catalytic hydrogenation with a nickel catalyst or treatment with iron in the presence of hydrochloric acid with heating; oxidation of alkylthio to alkylsulphinyloxy or alkylsulphonyloxy.

It will also be appreciated that in some of the reactions mentioned herein it may be 15 necessary/desirable to protect any sensitive groups in the compounds. The instances where protection is necessary or desirable and suitable methods for protection are known to those skilled in the art. Conventional protecting groups may be used in accordance with standard practice [for illustration see "Protective Groups in Organic Chemistry", edited by J.W.F.McOmie, Plenum Press (1973), and "Protective groups in Organic Synthesis", 2nd 20 edition, T.W Greene & P. G. M. Wutz, Wiley-Interscience (1991)]. Thus, if reactants include groups such as amino, carboxy or hydroxy it may be desirable to protect the group in some of the reactions mentioned herein.

A suitable protecting group for an amino or alkylamino group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an alkoxy carbonyl group, for example a 25 methoxycarbonyl, ethoxycarbonyl or *t*-butoxycarbonyl group, an arylmethoxycarbonyl group, for example benzyloxycarbonyl, or an aroyl group, for example benzoyl. The deprotection conditions for the above protecting groups necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or alkoxy carbonyl group or an aroyl group may be removed for example, by hydrolysis with a suitable base such as an alkali 30 metal hydroxide, for example lithium or sodium hydroxide. Alternatively an acyl group such as a *t*-butoxycarbonyl group may be removed, for example, by treatment with a suitable acid as hydrochloric, sulphuric or phosphoric acid or trifluoroacetic acid and an

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arylmethoxycarbonyl group such as a benzyloxycarbonyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon, or by treatment with a Lewis acid for example boron tris(trifluoroacetate). A suitable alternative protecting group for a primary amino group is, for example, a phthaloyl group which may be removed by treatment 5 with an alkylamine, for example dimethylaminopropylamine, or with hydrazine.

A suitable protecting group for a hydroxy group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an aroyl group, for example benzoyl, or an arylmethyl group, for example benzyl. The deprotection conditions for the above protecting groups will necessarily vary with the choice of protecting group. Thus, for example, an acyl 10 group such as an alkanoyl or an aroyl group may be removed, for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an arylmethyl group such as a benzyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

A suitable protecting group for a carboxy group is, for example, an esterifying group, 15 for example a methyl or an ethyl group which may be removed, for example, by hydrolysis with a base such as sodium hydroxide, or for example a *t*-butyl group which may be removed, for example, by treatment with an acid, for example an organic acid such as trifluoroacetic acid, or for example a benzyl group which may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

20 The protecting groups may be removed at any convenient stage in the synthesis using conventional techniques well known in the chemical art.

Certain intermediates in the preparation of a compound of the formula (1) are novel and form another aspect of the invention.

As stated hereinbefore the compounds defined in the present invention possesses 25 glycogen phosphorylase inhibitory activity. This property may be assessed, for example, using the procedure set out below.

Assay

The activity of the compounds is determined by measuring the inhibitory effect of the compounds in the direction of glycogen synthesis, the conversion of glucose-1-phosphate into 30 glycogen with the release of inorganic phosphate, as described in EP 0 846 464 A2. The reactions were in 96well microplate format in a volume of 100µl. The change in optical density due to inorganic phosphate formation was measured at 620nM in a Labsystems iEMS

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- Reader MF by the general method of (Nordlie R.C and Arion W.J, Methods of Enzymology, 1966, 619-625). The reaction is in 50mM HEPES (*N*-(2-Hydroxyethyl)piperazine-*N'*-(2-ethanesulfonic acid);4-(2-Hydroxyethyl)piperazine-1-ethanesulfonic acid), 2.5mM MgCl₂, 2.25mM ethylene glycol-bis(b-aminoethyl ether) *N,N,N',N'*-tetraacetic acid, 100mM KCl,
- 5 2mM D-(+)-glucose pH7.2, containing 0.5mM dithiothreitol, the assay buffer solution, with 0.1mg type III glycogen, 0.15ug glycogen phosphorylase *a* (GPa) from rabbit muscle and 0.5mM glucose-1-phosphate. GPa is pre-incubated in the assay buffer solution with the type III glycogen at 2.5 mg ml⁻¹ for 30 minutes. 40μl of the enzyme solution is added to 25μl assay buffer solution and the reaction started with the addition of 25μl 2mM glucose-1-phosphate.
- 10 Compounds to be tested are prepared in 10μl 10% DMSO in assay buffer solution, with final concentration of 1% DMSO in the assay. The non-inhibited activity of GPa is measured in the presence of 10μl 10% DMSO in assay buffer solution and maximum inhibition measured in the presence of 30μM CP320626 (Hoover et al (1998) J Med Chem, 41, 2934-8; Martin et al (1998) PNAS 95, 1776-81). The reaction is stopped after 30min with the addition of 50μl
- 15 acidic ammonium molybdate solution, 12ug ml⁻¹ in 3.48% H₂SO₄ with 1% sodium lauryl sulphate and 10ug ml⁻¹ ascorbic acid. After 30 minutes at room temperature the absorbency at 620nm is measured.

The assay is performed at a test concentration of inhibitor of 10μM or 100μM.

- Compounds demonstrating significant inhibition at one or both of these concentrations may be
- 20 further evaluated using a range of test concentrations of inhibitor to determine an IC₅₀, a concentration predicted to inhibit the enzyme reaction by 50%.

Activity is calculated as follows:-

$$\% \text{ inhibition} = (1 - (\text{compound OD620} - \text{fully inhibited OD620}) / (\text{non-inhibited rate OD620} - \text{fully inhibited OD620})) * 100.$$

- 25 OD620 = optical density at 620nM.

Typical IC₅₀ values for compounds of the invention when tested in the above assay are in the range 100μM to 1nM.

- The activity of the compounds is alternatively determined by measuring the inhibitory effect of the compounds on glycogen degradation, the production of glucose-1-phosphate from
- 30 glycogen is monitored by the multienzyme coupled assay, as described in EP 0 846 464 A2, general method of Pesce et al (Pesce, M A, Bodourian, S H, Harris, R C, and Nicholson, J F (1977) Clinical Chemistry 23, 1171 - 1717). The reactions were in 384well microplate format

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in a volume of 50 μ l. The change in fluorescence due to the conversion of the co-factor NAD to NADH is measured at 340nM excitation, 465nm emission in a Tecan Ultra Multifunctional Microplate Reader. The reaction is in 50mM HEPES, 3.5mM KH₂PO₄, 2.5mM MgCl₂, 2.5mM ethylene glycol-bis(b-aminoethyl ether) *N,N,N',N'*-tetraacetic acid, 100mM KCl, 8mM 5 D-(+)-glucose pH7.2, containing 0.5mM dithiothreitol, the assay buffer solution. Human recombinant liver glycogen phosphorylase *a* (hrl GP*a*) 20nM is pre-incubated in assay buffer solution with 6.25mM NAD, 1.25mg type III glycogen at 1.25 mg ml⁻¹ the reagent buffer, for 30 minutes. The coupling enzymes, phosphoglucomutase and glucose-6-phosphate dehydrogenase (Sigma) are prepared in reagent buffer, final concentration 0.25Units per 10 well. 20 μ l of the hrl GP*a* solution is added to 10 μ l compound solution and the reaction started with the addition of 20 μ l coupling enzyme solution. Compounds to be tested are prepared in 10 μ l 5% DMSO in assay buffer solution, with final concentration of 1% DMSO in the assay. The non-inhibited activity of GP*a* is measured in the presence of 10 μ l 5% DMSO in assay 15 buffer solution and maximum inhibition measured in the presence of 5mgs ml⁻¹ N-ethylmaleimide. After 6 hours at 30°C Relative Fluorescence Units (RFUs) are measured at 340nM excitation, 465nm emission .

The assay is performed at a test concentration of inhibitor of 10 μ M or 100 μ M. Compounds demonstrating significant inhibition at one or both of these concentrations may be further evaluated using a range of test concentrations of inhibitor to determine an IC₅₀, a 20 concentration predicted to inhibit the enzyme reaction by 50%.

Activity is calculated as follows:-

% inhibition = (1 - (compound RFUs - fully inhibited RFUs)/ (non-inhibited rate RFUs - fully inhibited RFUs)) * 100.

Typical IC₅₀ values for compounds of the invention when tested in the above assay are 25 in the range 100 μ M to 1nM. For example, Example 1 gave an IC₅₀ value of 0.55 μ m.

The inhibitory activity of compounds was further tested in rat primary hepatocytes. Rat hepatocytes were isolated by the collagenase perfusion technique, general method of Seglen (P.O. Seglen, Methods Cell Biology (1976) 13 29-83). Cells were cultured on Nunclon six well culture plates in DMEM (Dulbecco's Modified Eagle's Medium) with high level of 30 glucose containing 10% foetal calf serum, NEAA (non essential amino acids), Glutamine, penicillin /streptomycin ((100units/100ug)/ml) for 4 to 6 hours. The hepatocytes were then cultured in the DMEM solution without foetal calf serum and with 10nM insulin and 10nM

dexamethasone. Experiments were initiated after 18-20 hours culture by washing the cells and adding Krebs-Henseleit bicarbonate buffer containing 2.5mM CaCl₂ and 1% gelatin. The test compound was added and 5 minutes later the cells were challenged with 25nM glucagon. The Krebs-Henseleit solution was removed after 60 min incubation at 37°C , 95%O₂/5%CO₂ and 5 the glucose concentration of the Krebs-Henseleit solution measured.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of the formula (1), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore in association with a pharmaceutically-acceptable diluent or carrier.

10 The compositions of the invention may be in a form suitable for oral use (for example as tablets, lozenges, hard or soft capsules, aqueous or oily suspensions, emulsions, dispersible powders or granules, syrups or elixirs), for topical use (for example as creams, ointments, gels, or aqueous or oily solutions or suspensions), for administration by inhalation (for example as a finely divided powder or a liquid aerosol), for administration by insufflation (for 15 example as a finely divided powder) or for parenteral administration (for example as a sterile aqueous or oily solution for intravenous, subcutaneous, intramuscular or intramuscular dosing or as a suppository for rectal dosing).

20 The compositions of the invention may be obtained by conventional procedures using conventional pharmaceutical excipients, well known in the art. Thus, compositions intended for oral use may contain, for example, one or more colouring, sweetening, flavouring and/or preservative agents.

Suitable pharmaceutically acceptable excipients for a tablet formulation include, for example, inert diluents such as lactose, sodium carbonate, calcium phosphate or calcium carbonate, granulating and disintegrating agents such as corn starch or algenic acid; binding 25 agents such as starch; lubricating agents such as magnesium stearate, stearic acid or talc; preservative agents such as ethyl or propyl p-hydroxybenzoate, and anti-oxidants, such as ascorbic acid. Tablet formulations may be uncoated or coated either to modify their disintegration and the subsequent absorption of the active ingredient within the gastrointestinal tract, or to improve their stability and/or appearance, in either case, using 30 conventional coating agents and procedures well known in the art.

Compositions for oral use may be in the form of hard gelatin capsules in which the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium

phosphate or kaolin, or as soft gelatin capsules in which the active ingredient is mixed with water or an oil such as peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions generally contain the active ingredient in finely powdered form together with one or more suspending agents, such as sodium carboxymethylcellulose, 5 methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents such as lecithin or condensation products of an alkylene oxide with fatty acids (for example polyoxethylene stearate), or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters 10 derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and 15 hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives (such as ethyl or propyl *p*-hydroxybenzoate, anti-oxidants (such as ascorbic acid), colouring agents, flavouring agents, and/or sweetening agents (such as sucrose, saccharine or aspartame).

Oily suspensions may be formulated by suspending the active ingredient in a vegetable 20 oil (such as arachis oil, olive oil, sesame oil or coconut oil) or in a mineral oil (such as liquid paraffin). The oily suspensions may also contain a thickening agent such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set out above, and flavouring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

25 Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water generally contain the active ingredient together with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients such as sweetening, flavouring and colouring agents, may also be present.

30 The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, such as olive oil or arachis oil, or a mineral oil, such as for example liquid paraffin or a mixture of any of these. Suitable

emulsifying agents may be, for example, naturally-occurring gums such as gum acacia or gum tragacanth, naturally-occurring phosphatides such as soya bean, lecithin, an esters or partial esters derived from fatty acids and hexitol anhydrides (for example sorbitan monooleate) and condensation products of the said partial esters with ethylene oxide such as polyoxyethylene 5 sorbitan monooleate. The emulsions may also contain sweetening, flavouring and preservative agents.

Syrups and elixirs may be formulated with sweetening agents such as glycerol, propylene glycol, sorbitol, aspartame or sucrose, and may also contain a demulcent, preservative, flavouring and/or colouring agent.

10 The pharmaceutical compositions may also be in the form of a sterile injectable aqueous or oily suspension, which may be formulated according to known procedures using one or more of the appropriate dispersing or wetting agents and suspending agents, which have been mentioned above. A sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example a 15 solution in 1,3-butanediol.

Compositions for administration by inhalation may be in the form of a conventional pressurised aerosol arranged to dispense the active ingredient either as an aerosol containing finely divided solid or liquid droplets. Conventional aerosol propellants such as volatile fluorinated hydrocarbons or hydrocarbons may be used and the aerosol device is conveniently 20 arranged to dispense a metered quantity of active ingredient.

For further information on formulation the reader is referred to Chapter 25.2 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

The amount of active ingredient that is combined with one or more excipients to 25 produce a single dosage form will necessarily vary depending upon the host treated and the particular route of administration. For example, a formulation intended for oral administration to humans will generally contain, for example, from 0.5 mg to 2 g of active agent compounded with an appropriate and convenient amount of excipients which may vary from about 5 to about 98 percent by weight of the total composition. Dosage unit forms will 30 generally contain about 1 mg to about 500 mg of an active ingredient. For further information on Routes of Administration and Dosage Regimes the reader is referred to Chapter 25.3 in

Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

The compound of formula (1) will normally be administered to a warm-blooded animal at a unit dose within the range 5-5000 mg per square meter body area of the animal, 5 i.e. approximately 0.1-100 mg/kg, and this normally provides a therapeutically-effective dose.

A unit dose form such as a tablet or capsule will usually contain, for example 1-250 mg of active ingredient. Preferably a daily dose in the range of 1-50 mg/kg is employed. However the daily dose will necessarily be varied depending upon the host treated, the particular route of administration, and the severity of the illness being treated. Accordingly the optimum 10 dosage may be determined by the practitioner who is treating any particular patient.

The inhibition of glycogen phosphorylase activity described herein may be applied as a sole therapy or may involve, in addition to the subject of the present invention, one or more other substances and/or treatments. Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate administration of the individual components of the 15 treatment. Simultaneous treatment may be in a single tablet or in separate tablets. For example in the treatment of diabetes mellitus chemotherapy may include the following main categories of treatment:

- 1) Insulin and insulin analogues;
- 2) Insulin secretagogues including sulphonylureas (for example glibenclamide, glipizide) 20 and prandial glucose regulators (for example repaglinide, nateglinide);
- 3) Insulin sensitising agents including PPAR γ agonists (for example pioglitazone and rosiglitazone);
- 4) Agents that suppress hepatic glucose output (for example metformin).
- 5) Agents designed to reduce the absorption of glucose from the intestine (for example 25 acarbose);
- 6) Agents designed to treat the complications of prolonged hyperglycaemia;
- 7) Anti-obesity agents (for example sibutramine and orlistat);
- 8) Anti-dyslipidaemia agents such as, HMG-CoA reductase inhibitors (statins, eg 30 pravastatin); PPAR α agonists (fibrates, eg gemfibrozil); bile acid sequestrants (cholestyramine); cholesterol absorption inhibitors (plant stanols, synthetic inhibitors); bile acid absorption inhibitors (IBATi) and nicotinic acid and analogues (niacin and slow release formulations);

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- 9) Antihypertensive agents such as, β blockers (eg atenolol, inderal); ACE inhibitors (eg lisinopril); Calcium antagonists (eg. nifedipine); Angiotensin receptor antagonists (eg candesartan), α antagonists and diuretic agents (eg. furosemide, benzthiazide);
- 10) Haemostasis modulators such as, antithrombotics, activators of fibrinolysis and antiplatelet agents; thrombin antagonists; factor Xa inhibitors; factor VIIa inhibitors); antiplatelet agents (eg. aspirin, clopidogrel); anticoagulants (heparin and Low molecular weight analogues, hirudin) and warfarin; and
- 11) Anti-inflammatory agents, such as non-steroidal anti-inflammatory drugs (eg. aspirin) and steroid anti-inflammatory agents (eg. cortisone).

10 According to a further aspect of the present invention there is provided a compound of the formula (1), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore, for use in a method of treatment of a warm-blooded animal such as man by therapy.

15 According to an additional aspect of the invention there is provided a compound of the formula (1), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore, for use as a medicament.

According to an additional aspect of the invention there is provided a compound of the formula (1), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore, for use as a medicament in the treatment of type 2 diabetes, insulin resistance, syndrome X, hyperinsulinaemia, hyperglucagonaemia, cardiac ischaemia or obesity in a warm-blooded animal such as man.

20 According to this another aspect of the invention there is provided the use of a compound of the formula (1), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore in the manufacture of a medicament for use in the treatment of type 2 diabetes, insulin resistance, syndrome X, hyperinsulinaemia, hyperglucagonaemia, cardiac ischaemia or obesity in a warm-blooded animal such as man.

25 According to this another aspect of the invention there is provided the use of a compound of the formula (1), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore in the manufacture of a medicament for use in the treatment of type 2 diabetes in a warm-blooded animal such as man.

According to a further feature of this aspect of the invention there is provided a method of producing a glycogen phosphorylase inhibitory effect in a warm-blooded animal,

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such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (1).

According to this further feature of this aspect of the invention there is provided a method of treating type 2 diabetes, insulin resistance, syndrome X, hyperinsulinaemia, 5 hyperglucagonaemia, cardiac ischaemia or obesity in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (1).

According to this further feature of this aspect of the invention there is provided a method of treating type 2 diabetes in a warm-blooded animal, such as man, in need of such 10 treatment which comprises administering to said animal an effective amount of a compound of formula (1).

As stated above the size of the dose required for the therapeutic or prophylactic treatment of a particular cell-proliferation disease will necessarily be varied depending on the host treated, the route of administration and the severity of the illness being treated. A unit 15 dose in the range, for example, 1-100 mg/kg, preferably 1-50 mg/kg is envisaged.

In addition to their use in therapeutic medicine, the compounds of formula (1) and their pharmaceutically acceptable salts are also useful as pharmacological tools in the development and standardisation of *in vitro* and *in vivo* test systems for the evaluation of the effects of inhibitors of cell cycle activity in laboratory animals such as cats, dogs, rabbits, 20 monkeys, rats and mice, as part of the search for new therapeutic agents.

In the above other pharmaceutical composition, process, method, use and medicament manufacture features, the alternative and preferred embodiments of the compounds of the invention described herein also apply.

25 Examples

The invention will now be illustrated by the following non-limiting examples in which, unless stated otherwise:

(i) temperatures are given in degrees Celsius (°C); operations were carried out at room or ambient temperature, that is, at a temperature in the range of 18-25°C and under an 30 atmosphere of an inert gas such as argon;

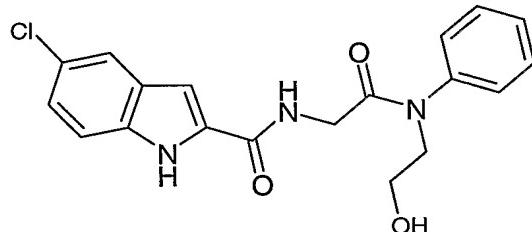
-27-

- (ii) organic solutions were dried over anhydrous magnesium sulphate; evaporation of solvent was carried out using a rotary evaporator under reduced pressure (600-4000 Pascals; 4.5-30 mmHg) with a bath temperature of up to 60°C;
- (iii) in general, the course of reactions was followed by TLC and reaction times are given for 5 illustration only;
- (iv) yields are given for illustration only and are not necessarily those which can be obtained by diligent process development; preparations were repeated if more material was required;
- (v) where given, NMR data is in the form of delta values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as an internal standard, 10 determined at 300 MHz using perdeuterio dimethyl sulphoxide ($\text{DMSO}-\delta_6$) as solvent unless otherwise indicated, other solvents (where indicated in the text) include deuterated chloroform CDCl_3 ;
- (vi) chemical symbols have their usual meanings; SI units and symbols are used;
- (vii) solvent ratios are given in volume : volume (v/v) terms;
- 15 (viii) mass spectra (MS) were run with an electron energy of 70 electron volts in the chemical ionisation (CI) mode using a direct exposure probe; where indicated ionisation was effected by electron impact (EI), fast atom bombardment (FAB) or electrospray (ESP); values for m/z are given; generally, only ions which indicate the parent mass are reported and unless otherwise stated the value quoted is $(M-\text{H})^-$;
- 20 (ix) The following abbreviations are used:

DMTMM	4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride
THF	tetrahydrofuran;

25 **Example 1**

5-Chloro-N-{2-[{(2-hydroxyethyl)phenylamino]-2-oxoethyl}-1*H*-indole-2-carboxamide



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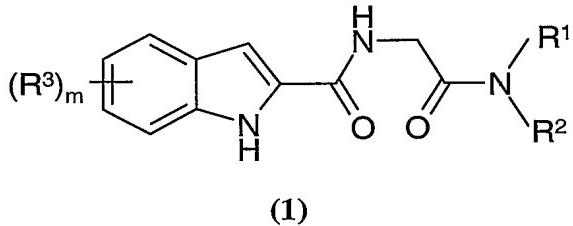
- A solution of *N*-(5-chloro-1*H*-indol-2-yl)carbonyl]glycine (Cas Reg No 186429-62-9; Hulin, Bernard, et al, PCT International Patent Application (1996) WO 9639384; 374 mg , 1.5mmol) and 2-(phenylamino)ethanol (228mg, 1.6mmol) in THF (20ml) was stirred at ambient temperature for 30 minutes. 4-(4,6-Dimethoxy-1,3,5-triazin-2-yl)-4-
5 methylmorpholinium chloride (DMTMM) (480mg, 1.6mmol) was added and the reaction mixture stirred at ambient temperature overnight, poured into water (15ml) and extracted with ethyl acetate (3x15ml). The organic extracts were combined and washed with 1N citric acid solution (15ml), sodium bicarbonate solution (15ml), dried over magnesium sulphate, filtered and concentrated to give the title product (471mg, 86%).
10 ^1H NMR 300 MHz: (DMSOd₆) 3.45 (q, 2H), 3.71 (m, 4H), 4.65 (m, 1H), 7.09 (s, 1H), 7.16 (dd, 1H), 7.44 (m, 6H), 7.68 (s, 1H), 8.57 (t, 1H), 11.74 (s, 1H); Mass Spectrum: M+Na⁺ 393.8.

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Claims

1. A compound of formula (1):

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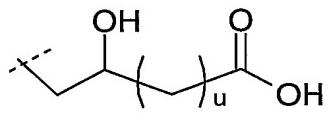
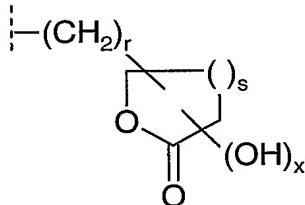
wherein:

R^1 is independently selected from C_{1-6} alkyl, C_{5-7} cycloalkyl, C_{5-7} cycloalkyl C_{1-3} alkyl,

C_{1-6} alkoxy, C_{5-7} cycloalkoxy, C_{5-7} cycloalkyl C_{1-3} alkoxy, heterocyclyl, heterocyclyl C_{1-3} alkyl,

- 10 heterocyclyloxy or heterocyclyl C_{1-3} alkoxy (wherein each of these groups is substituted on carbon by 1, 2 or 3 hydroxy groups, provided that there is no more than one hydroxy group on the same carbon atom and a ring carbon atom adjacent to a ring heteroatom is not substituted by a hydroxy group) and groups of the formula A or A':

15

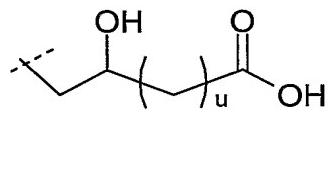
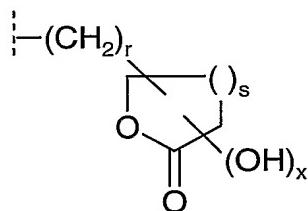


wherein x is 0 or 1, r is 0, 1, 2 or 3, s is 1 or 2 and u is 1 or 2; provided that in (A) the hydroxy group is not a substituent on the ring carbon adjacent to the ring oxygen;

R^2 is phenyl or heteroaryl (each of which is optionally substituted by 1 or 2 substituents independently selected from halo, cyano, trifluoromethyl, difluoromethyl, fluoromethyl,

- 20 C_{1-3} alkoxy, C_{1-3} alkanoyl, carbamoyl, $N\text{-C}_{1-3}\text{alkylcarbamoyl}$, $N,N\text{-di-C}_{1-3}\text{alkylcarbamoyl}$, sulfamoyl, $N\text{-C}_{1-3}\text{alkylsulfamoyl}$, $N,N\text{-di-C}_{1-3}\text{alkylsulfamoyl}$ and groups of the formulae B and B':

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wherein x is 0 or 1, r is 0, 1, 2 or 3, s is 1 or 2 and u is 1 or 2; provided that the hydroxy group is not a substituent on the ring carbon adjacent to the ring oxygen);

5 m is 0, 1 or 2;

R^3 is independently selected from hydrogen, halo, nitro, cyano, hydroxy, carboxy, carbamoyl, C₁₋₄alkyl, C₂₋₄alkenyl, C₂₋₄alkynyl, C₁₋₄alkoxy, C₁₋₄alkanoyl, fluoromethyl, difluoromethyl, trifluoromethyl and trifluoromethoxy;

provided that when R^1 is of the formula A or A' then R^2 does not contain a group of the

10 formula B or B' and when R^2 is of the formula B or B' then R^1 does not contain a group of the formula A or A';

or a pharmaceutically acceptable salt or prodrug thereof.

2. A compound of the formula (1) as claimed in claim 1, wherein:

15 R^1 is selected from C₁₋₆alkyl, C₅₋₇cycloalkyl, C₅₋₇cycloalkylmethyl, C₁₋₆alkoxy, C₅₋₇cycloalkoxy, C₅₋₇cycloalkylC₁₋₃methoxy, heterocyclyl, heterocyclylmethyl, heterocycloloxy and heterocyclylmethoxy (wherein each of these groups is substituted by 1 or 2 hydroxy groups provided that there is no more than one hydroxy group on the same carbon atom) or R^1 is of the formula A or A';

20 R^2 is a phenyl or heteroaryl group (each of which is optionally substituted by 1 or 2 substituents independently selected from halo, cyano, trifluoromethyl, carbamoyl, N-C₁₋₃alkylcarbamoyl, N,N-di-C₁₋₃alkylcarbamoyl, sulfamoyl, N-C₁₋₃alkylsulfamoyl, N,N-di-C₁₋₃alkylsulfamoyl, a group of the formula B and a group of the formula B'); or a pharmaceutically-acceptable salt or in-vivo hydrolysable ester thereof.

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3. A compound of the formula (1) as claimed in claim 1, wherein:

R¹ is selected from C₁₋₆alkyl, C₅₋₇cycloalkyl, C₅₋₇cycloalkylmethyl, C₁₋₆alkoxy, C₅₋₇cycloalkoxy and C₅₋₇cycloalkylC₁₋₃methoxy, (each group is substituted by 1 or 2 hydroxy groups provided that there is no more than one hydroxy group on the same carbon atom);

5 R² is a phenyl or heteroaryl group (each of which is optionally substituted by 1 or 2 substituents independently selected from halo, cyano, trifluoromethyl, carbamoyl, N-C₁₋₃alkylcarbamoyl, N,N-di-C₁₋₃alkylcarbamoyl, sulfamoyl, N-C₁₋₃alkylsulfamoyl and N,N-di-C₁₋₃alkylsulfamoyl);

or a pharmaceutically-acceptable salt or in-vivo hydrolysable ester thereof.

10

4. A compound of the formula (1) as claimed in claim 1, wherein:

R¹ is selected from ethyl, propyl, cyclopentyl, cyclohexyl, cyclopentylmethyl and cyclohexylmethyl (wherein each group is substituted by 1 or 2 hydroxy groups provided that there is no more than one hydroxy group on the same carbon atom);

15 R² is selected from phenyl, pyridyl, oxadiazolyl, oxazolyl, thiazolyl and thieryl (each of which group is optionally substituted by 1 or 2 substituents independently selected from halo, cyano, trifluoromethyl, carbamoyl, N-C₁₋₃alkylcarbamoyl, sulfamoyl and N-C₁₋₃alkylsulfamoyl);

m is 1; and

R³ is chloro;

20 or a pharmaceutically-acceptable salt or in-vivo hydrolysable ester thereof.

5. A compound of the formula (1) as claimed in claim 1 wherein:

R¹ is selected from 2-hydroxyethyl, 2,3-dihydroxypropyl, 3,4-dihydroxycyclopentyl and 3,4-dihydroxycyclopentylmethyl;

25 R² is phenyl optionally substituted by 1 or 2 substituents independently selected from halo, cyano, trifluoromethyl, carbamoyl, N-C₁₋₃alkylcarbamoyl, sulfamoyl and N-C₁₋₃alkylsulfamoyl;

m is 1 or 2; and

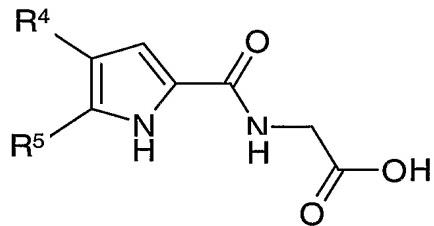
R³ is hydrogen or halo;

30 or a pharmaceutically-acceptable salt or in-vivo hydrolysable ester thereof.

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6. A process for preparing a compound of formula (1), as defined in claim 1 or a pharmaceutically-acceptable salt or an *in vivo* hydrolysable ester thereof which process comprises:

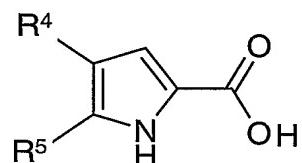
a) reacting an acid of the formula (2):



5

or an activated derivative thereof; with an amine of formula (3): HNR¹R² or

b) reacting an acid of the formula (4):



10

or an activated derivative thereof; with an amine of formula (5): H₂NCH₂CONR¹R² :

wherein R¹, R², R⁴ and R⁵ are, unless otherwise specified, as defined in claim 1;

wherein any functional groups are optionally protected;

and thereafter if necessary:

- 15 i) converting a compound of the formula (1) into another compound of the formula (1);
 ii) removing any protecting groups;
 iii) forming a pharmaceutically acceptable salt or *in vivo* hydrolysable ester.

7. A pharmaceutical composition comprising a compound of the formula (1) as claimed

- 20 in any one of claims 1 to 5 or a pharmaceutically-acceptable salt or *in vivo* hydrolysable ester thereof and a pharmaceutically-acceptable diluent or carrier.

8. A compound of the formula (1) as claimed in any one of claims 1 to 5, or a

pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, for use as a

- 25 medicament.

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9. The use of a compound of the formula (1), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as claimed in any one of claims 1 to 5, in the manufacture of a medicament for use in the treatment of type 2 diabetes, insulin resistance, syndrome X, hyperinsulinaemia, hyperglucagonaemia, cardiac ischaemia or obesity in a warm-blooded
5 animal.

10. A compound of the formula (1), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as claimed in any one of claims 1 to 5, for use as a medicament in the treatment of type 2 diabetes, insulin resistance, syndrome X, hyperinsulinaemia,
10 hyperglucagonaemia, cardiac ischaemia or obesity in a warm-blooded animal such as man.
11. A compound of the formula (1), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as claimed in any one of claims 1 to 5, in the manufacture of a medicament for use in the treatment of type 2 diabetes, insulin resistance, syndrome X, hyperinsulinaemia, hyperglucagonaemia, cardiac ischaemia or obesity in a warm-blooded
15 animal such as man.

12. A method of treating type 2 diabetes, insulin resistance, syndrome X, hyperinsulinaemia, hyperglucagonaemia, cardiac ischaemia or obesity in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal
20 an effective amount of a compound of formula (1) as claimed in any one of claims 1 to 5.

13. A method of treating type 2 diabetes in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (1) as claimed in any one of claims 1 to 5.

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(54) Title: INDOLE-AMIDE DERIVATIVES AND THEIR USE AS GLYCOGEN PHOSPHORYLASE INHIBITORS

(57) Abstract: Heterocyclic amides of formula (1) (A chemical formula should be inserted here - please see paper copy enclosed herewith) (1) wherein: R¹ is independently selected from, for example, C₁₋₆alkyl, C₅₋₇cycloalkyl, C₅₋₇cycloalkylC₁₋₃alkyl, C₁₋₆alkoxy, C₅₋₇cycloalkoxy, C₅₋₇cycloalkylC₁₋₃alkoxy, heterocyclcycl, heterocyclcycl, heterocyclcycl or heterocyclcyclC₁₋₃alkoxy; R² is phenyl or heteroaryl; R³ is independently selected from hydrogen, halo, nitro, cyano, hydroxy, carboxy, carbamoyl, C₁₋₄alkyl, C₂₋₄alkenyl, C₂₋₄alkynyl, C₁₋₄alkoxy, C₁₋₄alkanoyl, fluoromethyl, difluoromethyl, trifluoromethyl and trifluoromethoxy; or a pharmaceutically acceptable salt or pro-drug thereof; possess glycogen phosphorylase inhibitory activity and accordingly have value in the treatment of disease states associated with increased glycogen phosphorylase activity. Processes for the manufacture of said heterocyclic amide derivatives and pharmaceutical compositions containing them are described.

INTERNATIONAL SEARCH REPORT

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B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 96 39385 A (TREADWAY JUDITH L ;HULIN BERNARD (US); HOOVER DENNIS J (US); PFIZE) 12 December 1996 (1996-12-12) claims ---	1-13
A	WO 00 42213 A (UNIV NEW YORK) 20 July 2000 (2000-07-20) claims ---	1-13
P, A	WO 02 20530 A (FREEMAN SUE ;KENNY PETER (GB); MORLEY ANDREW (GB); WHITTAMORE PAUL) 14 March 2002 (2002-03-14) claims -----	1-13

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

° Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

26 September 2003

Date of mailing of the international search report

10/10/2003

Name and mailing address of the ISA

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Authorized officer

Chouly, J

INTERNATIONAL SEARCH REPORT

ational application No.
PCT/GB 03/00936

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 12,13 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
- No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 03/00936

Patent document cited in search report	Publication date		Patent family member(s)	Publication date
WO 9639385	A	12-12-1996	CA 2223625 A1 WO 9639385 A1 AP 624 A AT 205477 T AU 700887 B2 AU 5475396 A BG 62566 B1 BG 100635 A BR 9602626 A CN 1374082 A CZ 9601627 A3 DE 69522718 D1 DE 69522718 T2 DK 832066 T3 EP 0832066 A1 FI 974437 A GR 3037075 T3 HR 960266 A1 HU 9601285 A2 JP 11500445 T JP 3068200 B2 LV 11614 A LV 11614 B NO 962322 A NZ 286736 A PL 314603 A1 PT 832066 T RO 116963 B RU 2159613 C2 SG 45481 A1 SI 9600163 A SK 72096 A3 TR 970184 A1 TW 450961 B US 2002028810 A1 US 6297269 B1 ZA 9604646 A	12-12-1996 12-12-1996 19-12-1997 15-09-2001 14-01-1999 19-12-1996 29-02-2000 30-09-1997 01-09-1998 16-10-2002 11-12-1996 18-10-2001 07-02-2002 19-11-2001 01-04-1998 05-12-1997 31-01-2002 31-08-1997 28-09-1998 12-01-1999 24-07-2000 20-12-1996 20-04-1997 09-12-1996 27-07-2001 09-12-1996 28-12-2001 30-08-2001 27-11-2000 16-01-1998 28-02-1997 05-11-1997 21-03-1997 21-08-2001 07-03-2002 02-10-2001 05-12-1997
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